**Remarks**

Claims 1-20 were present in the application as filed. In response to a restriction dated September 21, 2006, Applicants elected the claims of Group I (claims 1-18). Claims 1-20 were pending with claims 19 and 20 withdrawn from consideration as being drawn to non-elected inventions. In response to the Office Action of September 11, 2008, claim 1 was amended and new claim 21 was added. Claims 19 and 20 are cancelled above and new claim 22 is added. Claims 1-18, 21 and 22 are pending in the application.

Step b) of claim 1 is amended to recite that anticoagulated whole blood and precipitating agent are mixed at room temperature initiating an incubation step that occurs at room temperature. Support for the amendment can be found in the specification at page 10, ¶ [0037]. Additionally, claim 1 is amended to indicate that the supernatant that is obtained from precipitation of whole blood is in a form that is suitable as a wound healing material. Support for the amendment is found in the specification at page 1, ¶ [0003], and page 16, ¶ [0049] et seq., for example. Lastly, new claim 22 is added. No new matter is added by the amendment.

The present invention relates to a point-of-care method for obtaining a coagulant directly from whole blood without the need for the clinically accepted plasma isolation step.

**Rejections under 35 U.S.C. §101**

Claims 1-18 and 21 are rejected under 35 U.S.C. §101 because, according to the Office Action, the subject matter claimed by independent claim 1 does not fall into a single statutory class of invention. Claim 1 is amended above to remove previously added step f); as amended the claim relates to a method of making a coagulant in a form suitable for use as a wound healing material.

Withdrawal of the rejection under 35 U.S.C. §101 is respectfully requested.

**Rejections under 35 U.S.C. §102**

Claims 1, 3, 4, and 12-16 are rejected under 35 U.S.C. §102(b) as being anticipated by Xiao et al. According to the Office Action, the method of Xiao inherently anticipates Applicants' claimed method.

***Xiao et al.***

Xiao et al. teaches a method for determining the levels of serotonin in anticoagulated whole blood. The method includes the steps of freezing and thawing the anticoagulated whole blood followed by deproteinization using perchloric acid followed by centrifugation and collection of the serotonin-containing supernatant, which also contains perchloric acid. The method steps including deproteinization were performed at 4°C (p. 506, 2nd column). Additionally, the method of Xiao et al. requires addition of internal standard to the whole blood prior to freezing. Furthermore, the method does not yield a supernatant in a form that is suitable for administration as part of a wound healing material, because of its perchloric acid content. Lastly, Xiao et al. does not teach or suggest that the supernatant retains coagulant activity. Xiao et al., therefore, teaches additional method steps not present in Applicants' claimed method and does not teach or suggest at least one element of Applicants' claimed method, that is, incubation of whole blood and precipitating agent at room temperature.

Since Xiao et al. does not teach or fairly suggest all the elements of the method as currently claimed, and in fact, includes additional steps (freezing and thawing) that are not desirable for the instant invention, Xiao et al. cannot anticipate the claims, as amended. Withdrawal of the rejection under 35 U.S.C. §102 in view of Xiao et al. is respectfully requested.

***Coelho et al.***

Claims 1, 7, 8, 11, 14, 15 and 17 are also rejected under 35 U.S.C. §102(e) as being anticipated by Coelho et al. According to the Office Action, Coelho et al. teach a method for extracting and then dispensing thrombin consisting of taking whole blood, sequestering prothrombin from the whole blood by addition of ethanol, and filtering to separate the precipitate from the supernatant. Applicants respectfully disagree.

According to the Office Action, the disclosure of a method for obtaining thrombin from whole blood appears in the claims of the Coelho et al. patent. Specifically, claims 17, 55, 97, 99, 103, 107, 112, and 116 are directed to a method of extracting thrombin from whole blood without first isolating plasma. The Coelho et al. reference, however, fails to anticipate the instant invention because Coelho et al. 1) does not teach all the steps of the claimed method and 2) is not enabled with respect to a method of extracting thrombin from whole blood as claimed in claims 17, 55, 97, 99, 103, 107, 112, and 116.

To be anticipating, a prior art reference must disclose each and every limitation of the claimed invention, must be enabling, and must describe the claimed invention sufficiently to have placed it in possession of a person of ordinary skill in the field of the invention. *In re Paulsen*, 30 F.3d 1475, 1478-79, 31 USPQ2d 1671, 1673 (Fed.Cir.1994) This means that a person of ordinary skill in the field could combine the description of the invention in the anticipatory reference with that person's own knowledge to make the claimed invention. *Elan Pharms., Inc. v. Mayo Found. for Med. Educ. & Research*, 346 F.3d 1051, 1055 (Fed.Cir.2003). Furthermore, "...[the] absence from the reference of any claimed element negates anticipation. *Kloster Speedsteel AB v. Crucible Inc.*, 793 F.2d 1565, 230 U.S.P.Q.2d 1051 (Fed.Cir. 1987)

As a preliminary matter, Coelho et al. fails to teach all the elements of Applicants' claimed method. Specifically, Coelho et al. fails to teach a step for separating the cellular and plasma protein precipitate from the supernatant following incubation of whole blood with precipitating agent.

Coelho et al. claims two different embodiments of a thrombin extraction method: one embodiment in which thrombin is extracted from plasma (claims 1-16, 18-54, 56-96, 98, 100-102, 104-106, 108-111, and 113-115) and another in which thrombin is extracted from whole blood (claims 17, 55, 97, 99, 103, 107, 112, and 116.) Applicants contend that with respect to Coelho's extraction of thrombin from plasma, the embodiment is enabled, but that the disclosure with respect to a thrombin extraction method using plasma as the starting material does not anticipate Applicants' invention.

Coelho et al. claims an alternative embodiment of the method that uses whole blood as the starting material without prior processing to remove cells (claimed in claims 17, 55, 97, 99, 103, 107, 112, and 116.) It is Applicants' position, however, that these claims represent the entire disclosure of a method for extracting thrombin using whole blood as the starting material and that the specification of Coelho et al., contains no guidance from which one of skill in the art, using his own knowledge of whole blood and its fractionation, would conclude that whole blood and plasma are interchangeable in the Coelho method.

Claim 17 of Coelho et al. reads as follows:

> 17. A method for extracting and then dispensing thrombin, the steps consisting of:
> taking whole blood from a person,
> sequestering prothrombin from the whole blood by addition of ethanol, wherein ethanol is present at a concentration between about 8% and 20% volume per unit volume,
> converting the prothrombin to thrombin,
> loading the thrombin into a syringe, and
> using the syringe to dispense the thrombin to stem blood flow.

Claim 17 of the Coelho et al. patent, by its closed transition language, teaches a method for extracting thrombin from whole blood by sequestering prothrombin using ethanol, and converting the prothrombin to thrombin. The thrombin is then loaded into a syringe for

subsequent dispensing.

The claim does not recite a step for removing the inevitable precipitate of cell debris and cellular protein components that results from mixing ethanol with whole blood, a phenomenon that does not occur with plasma since the blood's cellular component has already been removed. Moreover, the specification is silent as to why one would omit such a step. In essence, Coelho et al. teaches that the method causes the prothrombin to be sequestered but then the whole ethanol-treated gamische is added to the syringe without further processing. This does not anticipate Applicants' claimed method in which the cellular and protein precipitate is separated from the soluble faction containing the coagulant.

It is interesting to note that in the prosecution history of Coelho et al., the first appearance of claim 17, directed to a method of extracting thrombin from whole blood without a plasma isolation step, is in an amendment filed in response to the Restriction Requirement dated May 26, 2000. Because claim 17 (and the others directed to whole blood) were not part of the originally filed application, Applicants suggest that the specification as filed was not intended to encompass claims to a method of extracting thrombin from whole blood. The numerous references in the specification to *plasma* suggest that only the plasma embodiment was contemplated at the time the application was filed.

Coelho et al. teaches "preparing a fraction enriched in prothrombin by use of Ethanol to substantially enhance the concentration of prothrombin and at the same time *remove or denature naturally occurring ingredients within plasma*, such as Fibrinogen and Antithrombin III *which can bind to, block, interfere with or inhibit prothrombin or its subsequent activation to long-term functional thrombin*" (col. 6, lines 27-33). The disclosure of a method of extracting thrombin from whole blood without a precipitate removal step is, at best, inconsistent with the teachings of the specification, with respect to a method of extracting thrombin from plasma. According to Coelho et al., the purpose of the step of adding ethanol is to separate fibrinogen from the prothrombin, and to eliminate antithrombin III, which inhibits the formation of thrombin from prothrombin and which may inactivate the thrombin.

Throughout the specification, Coelho et al. refers to the sequestration of prothrombin and subsequent derivation of autologous thrombin *from plasma*, not whole blood (abstract; col. 6, lines 27-30; col. 6, lines 44-47; col. 7, lines 10-16; col. 7, lines 38-40; col. 9, lines 13-17.) Likewise, the description of Coelho's device for obtaining the thrombin repeatedly refers to plasma and not whole blood (col. 9, lines 7-10, lines 36-38, lines 47-50 etc.)

The specification, while it contains ample guidance with respect to the method using plasma as a starting material, is silent as to any additional considerations taking into account the significant differences between plasma and whole blood. The skilled artisan would recognize that whole blood and plasma represent distinctly different starting materials. Whole blood is a complex mixture of cells and extra-cellular constituents that remain relatively unaltered upon collection of the blood with an anticoagulant. 35-45% of the volume of whole blood is composed of red blood cells; 35% of the red blood cell is hemoglobin (Kevy Declaration ¶13, of record). Mechanical or chemical disruption of the red blood cells in whole blood, for example, by precipitation, generates considerable cell debris and results in release of hemoglobin into the prep.

Plasma, on the other hand, is the virtually cell-free supernatant of anticoagulated blood obtained after centrifugation to remove red blood cells. As indicated in the Declaration of Dr. Sherwin Kevy (of record), one of skill in the art would have known that precipitation of an anticoagulated whole blood preparation would result in a preparation containing significant levels of cell debris and cellular proteins not present in a similarly processed plasma preparation and therefore, would likely require different handling from plasma, in the event that the person of skill would even be motivated to use whole blood in the first place. Yet, Coelho, contains no disclosure of a filtering step when extracting thrombin from whole blood, nor is there any guidance on either the necessity or advisability of omitting the filtering step. Thus, the skilled artisan would likely conclude that the method steps using plasma would differ from the method steps using whole blood.

In response to the previous Office Action, Applicants argued that at the time of the invention by Applicants, isolation of plasma from whole blood prior to further processing was standard in the art for preparing fibrin sealant materials from blood. In support of this position, Applicants submitted three documents to establish the state of the art at the time of the invention.

Firstly, a Declaration Under 37 CFR §1.132 was submitted to establish the state of the art at the time the present application was filed; that is, that one of skill in the art would have recognized that precipitation of an anticoagulated whole blood preparation would result in a preparation containing significant levels of cell debris and cellular proteins not present in a similarly processed plasma preparation from which the cells have been removed (Declaration of Sherwin V. Kevy, M.D. June 13, 2007, ¶ 12) and that prior to 2006, no report of a method using whole blood without the plasma isolation step had been made; the standard of practice in the art for production of thrombin from whole blood included a plasma isolation step for the removal of cells/cell debris prior to precipitation of protein components, leaving soluble thrombin in the supernatant.

Additionally, Applicants submitted in support of the state of the art an article by ThermoGenesis (owner of Coelho patent) scientists, Kumar and Chapman, (JECT 39:18-23, 2007, already of record in the case) first reported generating autologous human thrombin from whole blood as the starting material (abstract). The Kumar reference represents the first disclosure of that which Applicants had already invented.

Lastly, Applicants submitted a brochure that elucidates the manner of using the device to perform the method claimed by Coelho et al.

In conclusion, Applicants' maintain that a method of extracting thrombin from whole blood without a plasma isolation step as disclosed in claims 17, 55, 97, 99, 103, 107, 112, and 116 of Coelho et al. is not enabled by the specification when viewed in light of the ordinary knowledge of one of skill in the art at the time.

Even if Coelho's claims to a whole blood were enabled, which they are not, Coelho et al. does not teach the step of separating the precipitate from the supernatant and recovering the supernatant (steps d) and e) of Applicants' claim 1) nor can one be imputed from the disclosure of a similar step in the plasma embodiment of the method. Moreover, given the state of the art at the time the Coelho et al. invention was made (as established by Applicants' earlier response), it is unlikely the skilled artisan would have sought to use whole blood in contradiction of the clinically accepted method for obtaining thrombin from. There is nothing in the literature to suggest that the use of whole blood without plasma isolation was contemplated.

Coelho et al. does not teach or fairly suggest a method for the extraction of thrombin by precipitation of whole blood and therefore, cannot anticipate Applicants' claimed method.

**Rejection under 35 U.S.C. §103**

Claims 1, 2, and 7-18 are rejected under 35 U.S.C. §103(a) as being unpatentable over Gray et al. (US 4,680,177) in view of Cochrum et al. (US 5, 773,033). Specifically, the Office Action asserts that one of skill in the art would have been motivated to substitute different methods of precipitation for cryoprecipitation in the method of Gray et al. with a reasonable expectation of success because Cochrum et al. teaches that these are art recognized equivalents for forming precipitates from blood. Applicants respectfully disagree.

Gray et al. relates primarily to the advantage of using neutral salts that do not bind calcium as anticoagulants in the collection of whole blood as opposed to conventional use of calcium-binding anticoagulants. Gray et al., however, appears to be cited in the Office Action for its teaching that anticoagulated whole blood can be fractionated by cryoprecipitation. This teaching is being combined with the teachings of Cochrum et al., which relates to a method for obtaining purified isolated fibrinogen from plasma. Cochrum et al. teaches that autologous fibrinogen is prepared from the patient's own blood which is *first separated into plasma, platelets and blood cells* (col. 10, lines 25-32.) The plasma is further processed by precipitation of fibrinogen under very stringent conditions using ammonium sulfate in an amount not to exceed 25% so that only fibrinogen is precipitated and there is no precipitation of other plasma

proteins. (col. 7, lines 53-56; col. 10, lines 6-10; col. 10, lines, 41-60.)

Blood fractionation methods are many and varied. The kind and conditions of precipitation affect the product obtained. Cryoprecipitation is not interchangeable with precipitation with a salt, such as ammonium sulfate, which is not interchangeable with precipitation with an organic material, such as ethanol. The Office Action position that optimization of conditions would be a matter of routine is unfounded. One of skill in the art would ***not*** have a reasonable expectation of success in obtaining the desired end product simply by substituting one precipitation method for another. This is particularly true if other variables are introduced, for example, using whole blood as the starting material rather than plasma. Thus, there is no apparent reason why one of skill in the art would combine the teachings of Cochrum et al. and Gray et al. and to achieve Applicants' invention, as currently claimed.

Claims 5 and 6 are rejected under 35 U.S.C. §103(a) as being unpatentable over Coelho et al. in view of Rock as applied to claims 1-4 and 7-18 and further in view of Sato et al. According to the Office Action, even though Coelho et al. does not teach anticoagulation of blood prior to use, it would have been obvious to do so based on the teachings of Rock et al.

The disclosure of Coelho et al. does not teach Applicants' claimed method for the reasons stated above.

Rock et al., describes a method for the stabilization of Factor VIII activity in whole blood or blood plasma by addition of a calcium-heparin solution, whereby calcium is restored to physiologic levels following anticoagulation of the blood with a calcium chelating anticoagulant. Rock et al. does not relate to the precipitation of either whole blood or plasma for the recovery of a coagulant material like thrombin. Rock et al. does not compensate for the deficiencies in the teachings of Coelho et al.

Claims 5 and 6 are rejected under 35 U.S.C. §103(a) as being unpatentable over Coelho et al. in view of Rock as applied to claims 1-4 and 7-18 and further in view of Sato et al. According to the Office Action, One of ordinary skill in the ar would have been motivated to add mannitol to the ACD anticoagulant in the method of Coelho et al. because Sato et al. teaches that by adding mannitol to blood, the swelling of blood cells can be prevented during the preservation.

Sato et al. describes the benefit of reduced hemolysis by adding glycerin and mannitol to a blood preservation solution.

To the extent that both Rock et al. and Sato et al. relate to anticoagulant preparations commonly used in the art, but not to mixing of whole blood with a precipitating agent to obtain a supernatant containing a coagulant, they do not compensate for the deficiencies in the teachings of Coelho et al.

None of the references cited herein teach or fairly suggest that a coagulant, for example, thrombin can be extracted from whole blood by precipitation of the whole blood without the intermediate plasma isolation step. The ultimate solution of a previously intractable problem can indeed appear to become apparent in hindsight after the final successful step is taken. Yet that final step in this case was not taken by those who came before, and was clearly not "obvious" to contemporaries, based on the subsequent peer review and publication of Applicants' claimed method in the scientific literature.

Withdrawal of the rejection under 35 U.S.C. §103(a) is respectfully requested.

**Double Patenting**

Claims 1, 3 and 4 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 16-18 and 20 of copending application

no. 11/200,535. The provisional rejection is duly noted with appropriate action to be taken upon allowance of the present claims or the '535 application.

It is respectfully submitted that the above-identified application is now in condition for allowance and favorable reconsideration and prompt allowance of these claims are respectfully requested. Should the Examiner believe that anything further is desirable in order to place the application in better condition for allowance, the Examiner is invited to contact Applicants' undersigned attorney at the telephone number listed below.

Respectfully submitted,

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